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09/853,688	05/14/2001	David N. Cooper	WCM78	6577

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,688	COOPER ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 30-39* is/are pending in the application.

4a) Of the above claim(s) *12-20,28 and 30-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Applicant's election with traverse of group I, claims 1-11, 21-27 and of the particular nucleic acid of SEQ ID NO: 35 (primer GH1F) in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the inventions of groups 1-IV are so closely related that a search and examination of the entire application can be made without a serious burden. Applicants state that a search of group I would yield all of the relevant prior art for the examination of groups II-IV. This is not found persuasive because it is maintained that undue burden would be required to examine the claims of groups II-IV along with the claims of group I. Restriction of related inventions is proper if it can be shown that the inventions have a different classification, or have acquired a separate status in the art or have a different field of search (see MPEP 808.02). The claims of groups I-IV have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter, such that the claims of group I are drawn to methods for detecting mutations in the GH1 gene, the claims of group II are drawn to nucleic acids, the claims of group III are drawn to GH1 variant proteins and the claims of group IV are drawn to methods for detecting GH1 variant proteins. Furthermore, it is maintained that each of the inventions are distinct for the reasons discussed in the previous Office action. A search of the distinct inventions would not be co-extensive as evidenced by the requirement for searching different keywords and nucleic acid and amino acid sequences and by the different classification of each invention. Therefore, undue burden would be required to examine each of the claimed inventions. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

It is noted that claims 21-27 depend from a non-elected claim (i.e, claim 12). In response to this office action, these claims should be amended so that they are limited to the subject matter which is currently being examined. In addition, it is noted that claim 23 is inclusive of methods of analyzing both GH1 nucleic acids and proteins. However, the claims have been examined only to the extent that they read on methods of analyzing GH1 nucleic acids and the subject matter of examining GH1 protein variants (group IV) has been withdrawn from consideration.

2. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR §1.821(d). See, for example, claim 11 and pages 11 and 40 of the specification.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 38). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. Claims 1-11 and 21-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting a variation in a GH1 nucleic acid, does not reasonably provide enablement for methods for detecting a variation in GH1 effective to act as an indicator of GH dysfunction in an individual or methods of identifying individuals having GH dysfunction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-11 are drawn to a method for detecting genetic variation in GH1 effective to act as an indicator of GH dysfunction. Claims 21-27 are drawn to methods for screening an individual suspected of GH dysfunction. The specification teaches improved methods for identifying mutations in the GH1 gene wherein the methods comprise comparing the sequence of a GH1 nucleic acid from a test sample with a standard GH1 nucleic acid sequence. The test samples are obtained from individuals who exhibit an abnormal height velocity, that is individuals who have a predicted adult height that is outside that of the individual's estimated adult height range, based on the height of the individual's parents. The specification teaches that the selection of test individuals based upon the above criteria provides a more sensitive means for identifying GH1 variants as compared to when test individuals are selected based only on the criteria of their height. Using this methodology, 54 new and distinct GH1 variants were identified, including 31 missense mutations, 21 mutations in the promoter/5' untranslated region, and 2 splice variants (see page 47). However, the specification also teaches that the method identified 71 polymorphisms in the GH1 gene region which are not associated with GH dysfunction (see for example pages 47-49). The claims as written require comparing a test sample nucleic acid to a "standard reference

sequence" and indicate that any difference between the test sample nucleic acid sequence and the standard reference sequence constitutes a "variation in GH1 effective to act as an indicator of GH dysfunction." However, since many of the alterations identified will constitute polymorphisms, the identification of a difference in the nucleotide sequence alone does not result in the identification of a variation in GH1 associated with GH dysfunction. The claims do not include any of the critical steps required to distinguish between polymorphisms and GH1 variants associated with GH dysfunction. As disclosed in the specification, additional research must be conducted to determine which of the identified variations in the GH1 gene are associated with GH dysfunction. There is no predictable means for distinguishing between the different types of variants without performing additional research to ascertain whether a mutation is associated with GH dysfunction.

Secondly, the claims require that the test sample is obtained from individuals who exhibit the criteria of "(i) growth failure, defined as a growth pattern [delineated by a series of height measurements; Brook CDG (Ed) Clinical Paediatric Endocrinology 3rd Ed....] which when plotted on a standard height chart [Tanner et al Arch Dis Child 45 755-762 (1970)], predicts n adult height for the individual which is outside the individual's estimated target adult height range." It is unclear as to whether the growth pattern and standard height chart require the specific teachings of Brook and Tanner or whether any growth pattern and height chart can be used to determine growth failure. Since the claims specifically reference these publications, it appears that this subject matter is essential to the claimed invention. However, the incorporation of essential material in the specification and claims by reference to a foreign application or patent,

or to a publication is improper. An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Accordingly, Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). Additionally, the claims must include all of the essential elements required to practice the claimed methods. The essential elements must be clearly set forth in the claims and cannot be incorporated into the claims by reference to a publication.

Thirdly, claims 21-22, and 24-27 require a comparison of a test nucleic acid with a nucleic acid which "was not detected by methods used hitherto, such as those reliant on patient selection criteria based primarily on absolute height." The claims do not clearly characterize the structure of the nucleic acid which meet the above criteria. What is intended to be encompassed by methods utilized prior to the present invention is not clearly defined in the specification and there is no predictable means for determining which mutations were known and by who these mutations were known prior to applicants invention. To claim an invention in terms of what it is not does not provide a clear and fixed definition of the invention and does not allow one of skill in the art to fairly practice the claimed invention without undue experimentation.

Accordingly, in view of the breadth of the claims and the lack of specific guidance and teachings in the specification, undue experimentation would be required to practice the claimed methods of detecting a variation in GH1 effective to act as an indicator of GH dysfunction and to practice the claimed methods of screening an individual suspected of GH dysfunction.

5. Claims 1-11 and 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite and vague because the claims are drawn to a method for detecting a variation in GH1 effective to act as an indicator of GH dysfunction, yet the claims recite only a final step of comparing a test sequence to a standard sequence. The claims do not clearly set forth how the step of comparing sequences results in the detection of a variation in GH1 effective to act as an indicator of GH dysfunction.

Claims 1-9, 11, 23 and 24 are indefinite and vague over the references to the Brook and Tanner publications. It is not clear as to whether the claims are intended to be limited to methods in which the individuals growth pattern is determined using the height measurements taught by Brook and height chart taught by Tanner or whether any height measurements and height chart may be used to determine the growth pattern. Additionally, the claims do not clearly set forth what is intended to be included by the height measurements of Brook and the height chart of Tanner and it is unclear as to how one uses the heights of the individual's parents to determine growth failure.

Claim 4 is indefinite over the recitation of "growth hormone function test". The specification (page 20) teaches that these tests refer to tests of growth hormone secretion. However, it is unclear if a normal result in a growth hormone function test requires that the individual secrete a "normal" amount of growth hormone or if the growth hormone that is secreted is functionally normal (i.e., the protein itself functions the same as the wild-type protein, but may be present in reduced quantities). Clarification of the claim is required.

Claims 6 and 10 are indefinite over the phrases "the four other paralogous (non-GH1) genes in the GH cluster" and "the homologous flanking regions in the four paralogous (non-GH1)" because these phrases lack proper antecedent basis. In addition, it is unclear as to what is intended to be encompassed by the homologous flanking regions.

Claim 11 is indefinite and vague over the recitation of "method further comprises the use of one or more primer(s)." The claim does not clearly set forth how the primers are used in the method of comparing the test and reference nucleic acids.

Claims 21-22, 24-27 are indefinite and confusing because the claims depend from two claims simultaneously. The methods of claims 1-27 require the use of a variant GH1 nucleic acid of claim 12, wherein the variant GH1 nucleic acid of claim 12 is obtained by performing the method of claim 1. It is improper for a claim to simultaneously depend from 2 different claims and as written it is unclear as to what sequence is being used as the predetermined sequence.

Claims 21-22 and 24-27 are further indefinite because it is unclear as to what is intended to be encompassed by the predetermined sequence. The claims define the predetermined sequence

in terms of what it is not, i.e. a sequence that "was not detected by methods used hitherto, such as those reliant on patient selection criteria based primarily on absolute height." There is no fixed definition in the art as to what sequences were not detected by methods "hitherto" and the claims do not clearly defined the sequences in terms of their structure so as to permit one of skill in the art to determine the meets and bounds of the claimed invention.

Claims 21-22, and 24-27 are indefinite over the recitation of "the corresponding region" and "corresponding gene" because "corresponding" is not an art recognized term to describe the relationship between two nucleic acid sequences. It is not clear whether this refers to sequence homology/similarity or to sequence complementarity and it is not clear what percentage of homology or complementarity is encompassed by "corresponding" or under what types of conditions "corresponding" nucleotides are determined.

Claims 21-27 are indefinite and unclear over the recitation of a "method for screening an individual suspected of GH dysfunction" wherein the method comprises comparing a test sample sequence to a predetermined sequence. It is unclear as to what the screening method is intended to accomplish. For example, it is unclear if the method is intended to be one for identifying an individual having GH dysfunction or if the method is one of screening for a new GH1 variant or if the method is one for screening for an individual whose nucleic acid contains a sequence identical to a previously identified GH1 variant.

Claims 24 and 25 are indefinite over the recitation of "the ..GH1 transcript" because this phrase lacks proper antecedent basis. While the claim previously refers to a GH1 gene, the claim

does not previously refer to a GH1 transcript. Claims 24-25 are further indefinite and confusing because the claim appears to include a step of comparing a first test sample to a second test sample, wherein the second test sample is identical to the predetermined sequence previously used in the claim for comparison to the test sample. It is unclear as to how steps (a) and (b) recited in claim 24 are intended to further limited claim 24 from claim 21. For example, are these steps performed in addition to or in place of the steps recited in claim 21? In addition, claim 21 already includes a step (a) and (b) and therefore if claim 24 is intended to include additional steps, these steps should be given a designation distinct from those used in claim 21.

Claims 26 and 27 are indefinite because it is unclear as to whether the claims intend to include an active process step of hybridizing test sample nucleic acid to an array comprising GH1 probes, or if the claims intend to only recite a means by which mutations could be detected, wherein the method does not necessarily require performing a method step using said means. The language "are used" and "by hybridization" are not considered to be active process steps. In addition, it is unclear as to what is intended to be encompassed by "all possible mutations". For example, does this refer to the fact that the array comprises fragments from the complete GH1 gene so that any mutation can be identified or does this mean that the array contains every possible GH1 mutant. However, in the later case, the specification does not clearly define all possible GH1 mutations and it is unclear as to what would be the structure of all possible GH1 mutations.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 10, 21-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamijo (Clinical Endocrinology (1999) 51: 355-360).

Kamijo (page 357) teaches methods for detecting the presence of genetic variation in the GH1 gene wherein the methods comprise obtaining a test sample containing the GH1 gene from an individual and comparing the GH1 gene sequence from said individual with the sequence of the wild-type GH1 gene. The individuals analyzed are characterized with respect to their heights and the heights of their parents (which were all within the average for the Japanese population) and did not have any other disorder that could be associated with growth failure (see pages 355-357). It is considered to be a property of the individuals analyzed in the method of Kamijo that these individuals have a growth failure in which their growth pattern predicts an adult height for the individual which is outside of the individual's estimated target adult height range, based upon the height of the individual's parents. It is noted that the claims do not require performing an actual step of estimating the target adult height of the individual based upon the growth pattern of the individual and the heights of the individual's parents. With respect to claims 6 and 10, Kamijo teaches methods of PCR amplification in which it is considered to be a property of the primers

that they are specific for the GH1 gene and do not cross-hybridize and amplify non-GH1 genes. With respect to claims 21, 22, and 24-25, the limitation that the variant was not detected by "methods used hitherto" does not distinguish the claimed invention over that of Kamijo because the method of Kamijo is considered to be a screening method capable of detecting any variant present in a GH1 nucleic acid, whether they were known or detected prior to the present invention.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 10, 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo (Clinical Endocrinology (1999) 51: 355-360) in view of Tanner (Archives of Disease in Childhood (1970) 45: 755-762).

This rejection is based on the interpretation of the claims as including a step of selecting test individuals based on the criteria that these individuals have a growth failure that is determined by considering both the height of the individual and the height of the individual's parents.

Kamijo(page 357) teaches methods for detecting the presence of genetic variation in the GH1 gene wherein the methods comprise obtaining a test sample containing the GH1 gene from an individual and comparing the GH1 gene sequence from said individual with the sequence of the wild-type GH1 gene. The individuals analyzed are characterized with respect to their heights and the heights of their parents (which were all within the average for the Japanese population) and did not have any other disorder that could be associated with growth failure (see pages 355-357). It is considered to be a property of the individuals analyzed in the method of Kamijo that these individuals have a growth failure in which their growth pattern predicts an adult height for the individual which is outside of the individual's estimated target adult height range, based upon the height of the individual's parents. It is noted that the claims do not require performing an actual step of estimating the target adult height of the individual based upon the growth pattern of the individual and the heights of the individual's parents. With respect to claims 6 and 10, Kamijo teaches methods of PCR amplification in which it is considered to be a property of the primers that they are specific for the GH1 gene and do not cross-hybridize and amplify non-GH1 genes.

With respect to claims 21, 22, and 24-25, the limitation that the variant was not detected by "methods used hitherto" does not distinguish the claimed invention over that of Kamijo because the method of Kamijo is considered to be a screening method capable of detecting any variant present in a GH1 nucleic acid, whether they were known or detected prior to the present invention. Kamijo teaches that the individuals that are analyzed for the presence of genetic variation have growth failure as defined by their height when plotted on a standard height chart and teaches that the parents for each of these individual's are in the normal height range. However, Kamijo does not teach measuring growth failure based on the criteria that these individuals have a growth failure that is determined based on the estimated target adult height of the individual and the height of the individual's parents.

Tanner teaches that the current standards for the height attained by a child at a given age make no allowance for the height of his or her parents (page 755 and 759). Tanner teaches improved methods for evaluating the height of children and of diagnosing children as having growth failure wherein the methods take into consideration the height of a child at a given age and the height of their fathers and mothers (page 756)

In view of the teachings of Tanner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamijo so as to have analyzed for genetic variation the GH1 genes of individuals characterized by having a growth failure, wherein said growth failure is determined by taking into consideration both the height of the individual and the height of the individual's parents, in order to have provided a more accurate

means for evaluating growth failure and which would have allowed for the inclusion of additional individuals which may have previously been excluded if the determination of growth failure was based on absolute height alone.

8. Claims 6, 7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo or Kamijo in view of Tanner and further in view of Miyata (Endocrine Journal (1997) 44: 149-154) cited in the IDS as reference "AK").

The teachings of Kamijo and Kamijo in view of Tanner are presented above. The combined references teach analyzing the GH1 gene for the presence of genetic variation by performing PCR amplification of all five exons and exon-intron junctions of the GH-1 gene and then sequencing the amplified GH1 nucleic acids (page 357). The references do not teach analyzing the entire GH1 gene of an individual by PCR amplification of the entire GH1 gene followed by nested PCR of overlapping GH1 fragments.

Miyata teaches methods for detecting the presence of genetic variation in the GH1 gene. In the method of Miyata, the complete region of GH1 genomic DNA was amplified by PCR (page 150-151). Following this amplification, nested primers were used to amplify overlapping subfragments of the first PCR product. Miyata also teaches using primers which are specific for the GH1 gene and which do not amplify any of the other components of the GH gene cluster.

In view of the teachings of Miyata , it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamijo so as to have also analyzed the human growth hormone gene for the presence of genetic variation using a

method which involved amplification with nested primers and primers that are specific for GH1 in order to have provided a more effective means for specifically amplifying the complete GH1 gene and identifying additional genetic variants that could be further analyzed for their association with growth failure.

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo or Kamijo in view of Tanner and further in view of Jin (Molecular Endocrinology (1999) 13: 1249-1266).

The teachings of Kamijo and Kamijo in view of Tanner are presented above. The combined references teach analyzing the GH1 gene for the presence of genetic variation. However, the references do not also teach analyzing the human growth hormone locus control for the presence of genetic variation.

Jin teaches the complete sequence of the human growth hormone locus control region (see, for example, figure 1) and teaches sequence analysis of this region (see page 1263). The reference also teaches that the presence of mutations in the control region that leads to decreased enhancer activity (see abstract and page 1259 and 1261).

In view of the teachings of Jin, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamijo so as to have also analyzed the human growth hormone locus control region for the presence of genetic variation in order to have identified additional GH1 variants that could be further analyzed for their association with growth dysfunction.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo or Kamijo in view of Tanner and further in view of O'Donovan (Genomics (1998) 52: 44-49; cited in the IDS as reference "AO").

The teachings of Kamijo and Kamijo in view of Tanner are presented above. The combined references teach analyzing the GH1 gene for the presence of genetic variation by performing PCR and then sequencing the amplified DNA or analyzing the amplified DNA by restriction enzyme analysis. The combined references do not also teach assaying for genetic variation by performing DHPLC.

O'Donovan teaches that DHPLC (denaturing high-performance liquid chromatography) is a highly sensitive, rapid, automatable and effective means for screening for mutations in a large number of sequences (see page 44). The reference further teaches methods of performing DHPLC (pages 44-45).

In view of the teachings of O'Donovan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamijo so as to have also analyzed the human growth hormone gene for the presence of genetic variation using the method of DHPLC in order to have provided a more rapid, automatable and highly sensitive means for screening a large number of samples for the presence of genetic variation.

11. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo or Kamijo in view of Tanner, each further in view of Miyata (Endocrine Journal (1997) 44: 149-154) cited in

the IDS as reference "AK"), as applied to claims 6, 7 and 10 above, and further in view of Chen (cited in the IDS as reference "AJ").

The teachings of Kamijo and Miyata and Kamijo in view of Tanner and Miyata are presented above. The combined references teach analyzing the GH1 gene for the presence of genetic variation by performing PCR amplification the complete GH-1 gene and followed by nested PCR of overlapping GH1 fragments. In particular, Miyata teaches analyzing the promoter region of the GH1 gene using primers which specifically amplify this region. Miyata teaches that PCR should be performed using primers which are specific for the GH1 gene and which do not amplify any of the other components of the GH gene cluster (page 150). The combined references do not teach performing PCR using the primer of present SEQ ID NO: 35, designated herein as "GH1F".

Chen teaches the complete sequence of the growth hormone cluster, including the sequence of each of the four GH genes in this cluster (see figure 2). Chen also compares the promoter sequences (figure 6) and mRNA sequences (figure 4) of each of the GH genes and identifies regions of sequence variability. In particular, the comparison of Chen readily identifies the regions of the promoter that are variable and the sequences that are unique to GH1, including those sequences which comprise present SEQ ID NO: 35 (see page 492/Figure 6, specifically the first three alignments).

In view of the teachings of Chen, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamijo so as to have

also analyzed the human growth hormone gene for the presence of genetic variation using a primer consisting of SEQ ID NO: 35 in order to have provided an effective means for amplifying the promoter region of GH1 and detecting genetic variation in the promoter region. The teachings in the prior art when considered as a whole would have lead the ordinary artisan to primers that specifically amplify the GH1 gene and particularly to the primer of SEQ ID NO: 35 because the teachings of Chen clearly establish that this region of the promoter is unique to GH1 and Miyata provides the guidance for selecting primers which are specific to GH1 and which do not amplify non-GH1 sequences.

12. Claims 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamijo or Kamijo in view of Tanner, each further in view of Hacia (Nature Genetics (1996) 14: 441-447).

The teachings of Kamijo and Kamijo in view of Tanner are presented above. The combined references teach analyzing the GH1 gene for the presence of genetic variation by performing PCR and then sequencing the amplified DNA or analyzing the amplified DNA by restriction enzyme analysis. The combined references do not teach assaying for genetic variation by using microarrays comprising probes to the GH1 gene.

Hacia (page 443-444) teaches methods for simultaneously detecting the presence of genetic variation in a gene. The method of Hacia involves the use of a high density oligonucleotide array and two color fluorescence analysis and allows for the rapid and accurate detection of heterozygous and homozygous mutations. Hacia characterizes the method as one

which provides a high-throughput, cost-efficient means for detection of genetic variation (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Kamijo so as to have also analyzed the human growth hormone gene for the presence of genetic variation using the method of microarray analysis taught by Hacia in order to have provided a rapid, accurate and cost-efficient means for simultaneously screening a large number of samples for the presence of genetic variation in the GH1 gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER

February 10, 2003